

Natural history of chronic asthma and its long-term effects on pulmonary function

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Although asthma is a disease that has intrigued physicians since antiquity, its natural history has been incompletely determined. It has long been held that the presence of asthma, *per se*, does not carry with it any long-term deterioration in lung function, but recently this view has been challenged, and it has become fashionable to define asthma as being only partially reversible. At present, there are limited data to support such a view. All of the available information indicates that the vast majority of patients do not experience the development of a progressive decline in pulmonary mechanics or appear to be at risk for a diminution in life expectancy. (*J Allergy Clin Immunol* 2000;105:S535-9.)

Key words: *Asthma, natural history, morbidity, mortality, long-term studies on lung function*

For many years, it has been taught that asthma is a disease characterized by reversible airway obstruction. Recently, however, it has become fashionable to think of this illness as having components that are potentially irreversible, and several consensus reports now define asthma in this fashion.^{1,2} The concerns about irreversibility, although important, are largely theoretic, and the data on which these conclusions are drawn are quite sparse.^{3,4} For example, other than a description of the phenomenon, little information is available about its prevalence or outcome. The purpose of this article is to explore what is known about the natural history of asthma as viewed from the perspective of the long-term effects on pulmonary function.

ASTHMA AS A CAUSE OF CHRONIC AIRWAY OBSTRUCTION

The factors at work in the development of asthma and those factors that control the structural consequences of inflammation have been presented earlier and will not be reviewed here. Suffice it to say that the events involved in the repair and remodeling of the bronchi have raised concerns that asthma could conceivably produce chronic changes in airway morphologic condition that could ultimately result in permanent, or poorly alterable, abnormalities in lung function that worsen with time. If this is

the case, then affected individuals may be at risk for increased morbidity and/or death. In such situations, early intervention would be essential to forestall or eliminate this process.

One means of directly testing such a hypothesis would be to follow a cohort of patients with asthma from the onset of their disease to death by the performance of serial measurements of pulmonary function. That information could then be related to the mortality rates attributable to the disease, quality of life indices, and the overall socioeconomic impact. One could then intervene at various points to determine the influences of different therapies on outcome. Obviously, such a study is not practical, or even feasible, in the industrialized world. Not only would it be logistically difficult, but the data would potentially be contaminated by existent physician biases. In many countries, it is now virtually impossible to find patients with asthma who have not received 1 or more of the medications touted as preventing chronic changes. Thus negative findings could not be interpreted with ease. Such an investigation could conceivably be performed with fruitful results, however, in emerging nations or in recent immigrants from such regions. In these populations, reliance is often placed on folk remedies of unproven worth,⁵ and preventative medications are not frequently used because of their lack of immediate effect and cost.

In the absence of data from direct appraisals, investigators have attempted to detect any potential negative impact of asthma by such stratagems as evaluating morbidity and mortality rates and relating that to functional status, examining pulmonary function longitudinally over the short-term or undertaking cross-sectional studies of symptoms and lung mechanics at specific points in time in large groups of patients. The relative merits and shortcomings of these approaches are presented.

Morbidity and death

The morbidity of asthma is enormous, but the factors that influence it are poorly delineated.⁶ It is estimated that approximately, \$6 billion each year are spent in the care of individuals with this illness. Although such data are impressive, they do not give major insights into the natural history. No one has differentiated whether symptomatic episodes and their associated costs derive from progressive disease, a lack of response to treatment, the unavailability of care, failure to take medication, or to other factors that have not yet been explored. It is now beginning to be appreciated that the morbidity of asthma in an epidemiologic sense is skewed and much of the medical use is accounted for by a relatively small per-

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centage of patients.^{7,8} The formal existence of these individuals has only recently been recognized, and the nature of their disease has not been fully ascertained. In the limited number of patients who have been treated aggressively and followed, the functional abnormalities are reversible.⁸

In general terms, there is no aspect of asthma morbidity from which one can conclude that the disease is progressive, rather circumstantial evidence suggests that it is not. If the natural history of asthma was similar to chronic bronchitis or cystic fibrosis (diseases that inexorably worsen with time and have high mortality rates), one would expect to find an ever-increasing percentage of individuals experiencing the development of accelerating clinical and physiologic impairments. This situation has not been found despite being repetitively sought. Because the numbers of patients with asthma in the United States run into the millions, even a 5% incidence of such events would produce tens of thousands of affected individuals; thus if such an effect existed, it must be uncommon to rare, because it is unlikely to be missed.

The data on death are even less helpful. On the surface, the subject seems straightforward, and one would think that it would be an easy matter to relate disease severity and/or progression and death. Unfortunately this is not the case. The available global data on asthma fatalities for the last 30 years show that mortality rates in the United States and Canada are lower than in other areas and are something less than 2 cases per 100,000.^{1,2} Despite the observance that deaths increased from 1.3 to 1.9 per 100,000 in the last decade in the United States,² the actual number of individuals with asthma who die is still quite small. In fact, 1 recent population study has not found any impact of asthma on expected longevity.⁹ Consequently, even in patients with asthma, the disease is not a common cause of death. To put the matter into perspective, according to the US Center for Disease Control,¹⁰ there were 10.3 million individuals with asthma and 5106 deaths from asthma in 1991. This means that 1 of every 2000 people at risk would have been affected. In the same time period, there were 85,544 deaths from chronic obstructive lung disease with a case mortality rate of 18.6 per 100,000 persons.¹² Thus the mortality data do not support the notion that asthma produces a progressive decline in lung function that ultimately leads to the patient's death.

Short-term longitudinal observations

It is well established that the mechanical properties of the lungs of normal nonsmokers begin to diminish somewhere around age 35 years.¹¹ In most people the loss occurs uniformly with the FEV₁ value declining by 25 to 30 mL/year. Various diseases can accelerate this process and eventually lead to respiratory insufficiency. The risk factors accepted by all investigators as being associated with an excessive rate of loss are cigarette smoking, cystic fibrosis, α -antitrypsin deficiency, and suppurative lung diseases such as bronchiectasis.¹² Some of the conditions that have been postulated as possibly increasing

the risks include childhood respiratory infections, allergy, and nonspecific airway hyperreactivity.^{12,13} Thus far, epidemiologic studies have not implicated asthma. The strengths of the arguments for and against the first 2 items have been reviewed and will not be recapitulated. It seems fair to conclude, however, that the information gathered to date in support of these events is not sufficiently robust to preclude further research.

A number of investigations have examined the tenant that airway hyperreactivity, per se, may be causally linked to an increased loss of lung function over time.¹³ In the main, these data are not very compelling. Although it is true that all of the epidemiologic studies indicate that increased bronchial responsiveness can be correlated with airway narrowing, the physiologic interpretation of such findings is far from clear, and a cause and effect relationship cannot be deduced. The reason for this state of affairs is that preexisting constriction virtually guarantees a positive statistical response to nonspecific pharmacologic stimuli independent of any intrinsic pathology.¹⁴ The smaller the airway before a given challenge, the less agonist it takes to reduce its diameter a fixed amount, so the greater likelihood of a false-positive result. Few studies have bothered to separate the relative impact of these confounding influences.

Although airway hyperreactivity is a prominent feature of asthma, the earlier notions that this factor is causally related to disease development or plays a pathogenetic role that requires treatment have been challenged.¹⁴ It is now generally accepted that asthma can wax or wane independent of changes in reactivity and vice-versa.¹⁴⁻¹⁶ Further, there is now a large amount of literature (19 studies involving 384 subjects) that has failed to establish a relationship between the degree of bronchial hyperresponsiveness and the value of the FEV₁ or the level of disease activity.¹⁴ In addition, long-term follow-up of individuals with asthma has not shown any association between temporal changes in forced expiratory volumes or flow rates and the level of airway reactivity.¹⁶ Finally, there are no data that relate bronchial hyperreactivity to death, the magnitude of pulmonary reserves, or the degree of reversibility of existing physiologic abnormalities.

The issue as to whether asthma, independent of bronchial hyperresponsivity, is a risk factor for the development of irreversible airway obstruction is also not yet settled. Dr Burney's suggestions that neither self-reported symptoms nor doctor-diagnosed asthma uniformly equate with the presence of the disease are prescient. Some investigators use the history of wheezing and dyspnea as incontrovertible evidence of the diagnosis of asthma without attempting to exclude other obstructive syndromes. This can be a great mistake particularly in the young and old.

There are only a few longitudinal investigations that have contrasted the pulmonary function in subjects with asthma and healthy subjects over time that suggest the possibility that asthma causes an exaggerated loss of lung function.¹⁷⁻¹⁹ These data were gathered at a time when

less was known of the natural history of the obstructive pulmonary syndromes, and they may be contaminated by the presence of confounding factors. Fletcher et al¹⁷ identified 17 individuals with doctor-diagnosed asthma who were followed for 8 years. Most of these subjects were smokers, or former smokers, and the rate of decline in the FEV₁ value in this group was slightly greater than in asymptomatic nonsmokers. Schachter et al¹⁸ in a survey of rural community residents concluded that some adults with asthma experienced a more rapid loss of FEV₁ value than did residents without asthma. Their data were not adjusted for smoking history, initial FEV₁ value, or age. Peat et al¹⁹ collected information over an 18-year period in a random population in Australia. In their sample, the FEV₁ values of the subjects with asthma decreased more rapidly than the subjects without asthma. The differences between groups were small (approximately 15 mL/y) and were not adjusted for the initial levels of FEV₁. Those subjects who smoked had the greatest effects.

Although it is true that asymptomatic patients with asthma have abnormalities in pulmonary mechanics and gas exchange,^{20,21} such observations do not necessarily mean that the changes are irreversible. The commonest finding in cross-sectional studies is the reduction of the flows in the mid-vital capacity range, an elevated residual volume, and an enlarged alveoloarterial gradient for oxygen.^{20,21} It is not established, however, whether these abnormalities represent incomplete resolution of recent episodes, the presence of low-grade ongoing disease, or permanent obstruction. The latter possibility is frequently mentioned in guidelines,^{1,2} but there are relatively little supporting data. Perhaps the best information is contained in the work of Brown et al.³ To determine whether asthma alone could cause irreversible airflow obstruction, these investigators treated 42 men and 47 women with theophylline and β -agonists for 4 weeks. Those in whom the FEV₁ level did not increase to 85% of predicted were then given a course of prednisolone. The authors found a relationship between the duration of the asthma and its severity at the beginning of the study. The correlation, however, was poor and accounted for less than 50% of the variability. Of interest, every subject improved after 4 weeks of treatment; and the mean FEV₁ level, even in those who required steroids, approached 76% of predicted. Longitudinal observations were not made, and it is unknown whether further aggressive management would have completely normalized mechanics.

LONG-TERM STUDIES ON LUNG FUNCTION IN ASTHMA

In the last decade, a number of long-term follow-up studies on patients with asthma that incorporate sequential measurements of pulmonary function have appeared.^{16,22-27} Although these data are informative, they unfortunately shed little direct light on such seminal issues as disease progression and irreversibility. Questions about whether lung function decreases in excess of

normal rates in patients who remain symptomatic for long periods and whether persistent disease activity is due to fixed obstruction remain unanswered. What is apparent is that the presence of asthma does not confer the same ominous risks to affected individuals as do other forms of obstructive lung disease.¹¹ For example, advancing age does not increase morbidity or mortality rates, and the outcome of childhood asthma followed to mid-adult life is quite favorable. Typically, the amount of wheezing in adolescence seems to be a guide for disease severity in later life. In 1 investigation, 323 patients with asthma were prospectively studied from the age of 7 to 28 years. Seventy-three percent of those patients with few symptoms at age 14 years had little or no wheezing at age 28 years.²² Alternatively, 68% of those with frequent wheezing as adolescents still had active disease as adults. In another trial, only 43% of 101 adults who had asthma as children were still symptomatic 20 years later.²³ Subjects with current symptoms had lower FEV₁ values than their asymptomatic counterparts. Because the symptoms of asthma, unlike those of chronic bronchitis, develop in association with decrements in lung function, this finding is not unexpected and cannot be equated with either a poor prognosis or the existence of fixed bronchial narrowing.

In terms of the type of changes in airway mechanics that occur over time, Ulrik et al²⁴ serially studied subjects with extrinsic and intrinsic asthma over 10 years. Those with nonallergic intrinsic illness had an annual decline of FEV₁ level of 50 mL whereas in the extrinsic group, the change was within the normal range (22 mL/y). Given that most authorities feel that intrinsic asthma has a pathogenesis that shares features with chronic bronchitis, this dichotomy is not surprising and confirms other works.^{11,28} In a more extensive study, Panhuysen et al²⁵ followed 189 patients with asthma over a quarter of a century and found pulmonary function actually to rise with the passage of time. The mean value for the FEV₁ was 64.1% of predicted initially whereas at the second visit 25 years later, it had increased to 71.5%. The long-term relationship between the intensity of symptoms in childhood and lung function as an adult has also been examined.^{16,26} Here, too, the results do not support the notion of progressive deterioration. The Department of Thoracic Medicine of the Royal Children's and the Royal Melbourne Hospitals measured pulmonary function at 14- and 21-year follow-up in a large group of children with asthma.^{16,26} The subjects were stratified into 4 groups according to their current symptoms (ie, no episodes within 3 years; no wheezing within 3 months; wheezing within 3 months but symptoms not acute or persistent; wheezing 1 or more times per week or persistent wheezing during the year before examination). At age 21 years (14-year follow-up; n = 342 patients),²⁷ the investigators noted a relationship between the severity of the patients' symptoms and their lung function as compared with control subjects. However, even the individuals with the most active disease still had a mean FEV₁ value that was 80% of predicted. Equally importantly, no

significant changes in the mean FEV₁ values were found in any group between the 14- and 21-year follow-up. In fact, the most severely ill patients had a significant increase in the FEV₁/FVC ratio during this time, and most subjects with an abnormal ratio and/or FVC had normal values at 21 years of age. At the next evaluation at age 28 years,²⁶ 286 subjects had pulmonary function measured. As before, the more symptomatic participants had lower values than control subjects, but groups 3 and 4 were not different from each other, and the functional data for the mild and maximally symptomatic groups differed little. Indeed, the authors make note of the low prevalence of abnormalities in the latter population. It is also apparent from the composite data that the mean FEV₁ level was higher for each group than it was at earlier times. There was no evidence of fixed obstruction found. All subjects whose initial FEV₁ was less than 70% of predicted improved at least 15% after the use of a bronchodilator. The authors reported that the group with the most symptoms at age 28 years (group 4) showed a steeper decline in the FEV₁/FVC ratio from age 10 years than did the other subjects, suggesting progressive decline. Although this is a worrisome observation, it must be tempered by the realization that this effect was not reported with any of the other variables, suggesting that it was an isolated finding of marginal significance.

Strachan et al²⁷ assessed the impact of past and current asthma on ventilatory function in a cohort of subjects followed from birth to ages 7, 11, 16, 22, and 33 years. Among 509 cases reporting wheezing within the past year, the FEV₁ level and the FEV₁/FVC ratio were reduced to a greater extent in those subjects with an earlier age of onset of symptoms, and the changes were alleged to be only partially reversed by the inhalation of albuterol. The authors interpreted these observations as indicating the presence of fixed obstruction that worsened with time. Reanalysis yields less certitude. The authors chose to express their data as a percentage of the recordings made in a concurrently followed control group, rather than as percentage of predicted norms; hence, the magnitude, or severity, of the abnormalities found cannot be ascertained. This is truly unfortunate because the differences observed for the index variables between those subjects with early and late onset symptoms were minor (ie, Δ FEV₁, approximately 6%; Δ FEV₁/FVC, approximately 4%). Similarly, the variability in the bronchodilator responses were also physiologically trivial. It is of great interest that the subjects who had not been wheezing within the last year ($n = 551$ subjects) had better lung function, irrespective of the age of onset, suggesting that ongoing disease activity rather than progressive pulmonary changes accounted for the results.

Perhaps the most extensive observations on the natural history of asthma are those of Panhuysen et al.²⁵ This work was based on a 25-year follow-up of 181 patients. At the end of the observation period, only 54% of the patients had heightened bronchial reactivity, a depressed FEV₁ level, and asthma symptoms. Twenty-one percent

of the patients were free of bronchial reactivity; 25% had FEV₁ values of more than 90% of predicted; 40% were asymptomatic, and 11% were judged to have lost their disease totally. The absence of asthma after 25 years was associated with the younger age and less severe airway obstruction at first testing. The absence of bronchial hyperreactivity was associated with a younger age, a higher FEV₁ level, and a shorter untreated period. The authors concluded that early intervention was important and that the less time a patient spent in an untreated state, the better off their disease would ultimately be. Although these are an interesting set of observations, it is important to realize that there are no control subjects. This is a serious omission because patients with asthma frequently deny symptoms, and even the existence of their disease, on repeat examinations^{18,27} and are notoriously unfaithful with their therapeutic regimens.²⁹ Without appropriate controls, there is no way of knowing whether or not the same things would have been found if the patients had been simply followed without the various interventions that the physicians used.

SUMMARY

The natural history of asthma is not yet resolved. Some patients appear to have an element of irreversibility, but the significance of this finding regarding morbidity and mortality rates is unknown, as is its prevalence. The available data suggest that the vast majority of individuals do well with their disease. The challenge remains as to whether one should treat to prevent potential irreversibility in all patients or only those few patients who may be at risk.

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